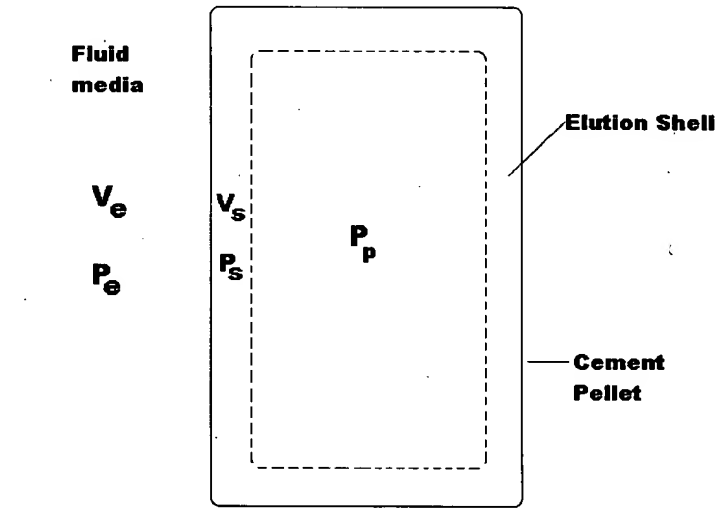
Drug Elution comparison

A simplified diagram of the polymerized PAM-PMMA cement pellet used in the leaching studies and placed within the leaching fluid is shown in Figure below. From this figure, the mass balance relationship of PAM within the leaching fluid at any time t is given by equation 1:

$$P_e * V_e = \delta * V_s * (P_p - P_s) \qquad (1)$$



where P_p = concentration of pamidronate in the polymerized PMMA test pellet (grm PAM/grm cement); P_s = concentration of pamidronate in the leaching shell (grm PAM/grm cement); V_s = volume of the leaching shell(ml); V_e = volume of leaching fluid(ml); P_e = concentration of pamidronate in leaching fluid (grm PAM/cc fluid); and δ = density of polymerized cement(grm cement/cc cement).

The ordinary differential equation 2 describes the rate of drug leaching out of the pellet and moving into the surrounding fluid:

$$V_e * \frac{dP_e}{dt} = k * P_s * \delta * V_s \qquad 2.$$

where k = leaching rate constant. We next rearrange equation 1 in terms of P_s and combine with 2. to eliminate P_s. This equation along with the initial condition, i.e. at t=0, P_e = 0, is solved resulting in equation 3. that estimates the concentration of PAM within the fluid surrounding the test pellet at time ,t:

$$P_e(t) = P_p * \frac{V_s}{V_e} * \delta * \left(1 - e^{-k*t}\right) \qquad 3.$$

Now at t=∞, P_e = P_{max} (grms Pam/cc fluid), the total amount of PAM that will leach out from the test pellet. Using this equation we can determine the leaching shell volume as

$$V_s = \frac{P_{max} * V_e}{P_p * \delta} \qquad 4.$$

The leaching shell thickness, □.. associated with V_s for the test pellet's cylindrical geometry is determined using equation 5 where R_p, H_p and V_p are the pellet's radius, height, and volume, respectively.

$$V_s = V_p - \pi * (R_p - \xi)^2 * (H_p - 2 * \xi) \qquad 5.$$

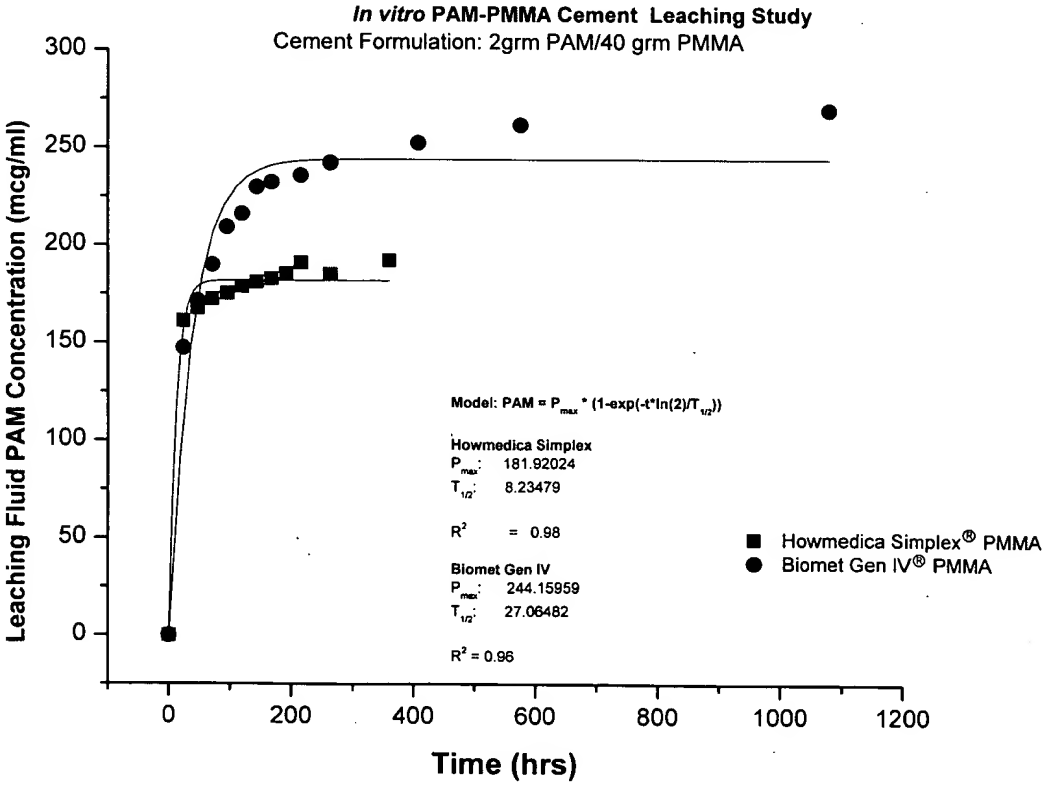
The shell thickness parameter, ξ. can be computed using an iterative solver such as SOLVER®, as implemented in MS Excel

XP. The drug delivery potential of the PAM-PMMA cement formulation is approximated using the following relation:

$$D_p = (P_{max} * V_e)/S_a \qquad 6.$$

where D_p = drug delivery potential (μgrms/cm^2) and S_a is the surface area of the test pellet (cm^2).

The results of leaching studies using Howmedica Simplex and Biomet Gen IV PAM-PMMA cements are presented in the Figure below. The leaching kinetic parameter, k, can also be expressed as $T_{1/2} = \ln(2)/k$ to express the delivery rate in terms of half-life.



From this leaching data and equations 5 and 6, we estimate that the test pellets of the PAM - Simplex® PMMA formulation

had a leaching shell thickness of 41.6μ, a delivery half-life of 8.24 hrs and drug delivery potential of 173μgrm/cm^2 while the PAM - Gen IV® PMMA leaching had a shell thickness was 133μ, a delivery half-life of 27 hours and drug delivery potential of 501μgrm/cm^2.

For the 2 gram drug/40 grm PMMA formulation we note that the average weight of the test pellet is 0.375 grams. Since the drug content is 0.0329grm/grm pellet, each pellet contains 12.3 mg drug. From the elution study, .737 mg drug leached out per pellet. This corresponds to 0.737/12.3 = 6% of drug leached out or 94% remains trapped. The larger the cement volume the greater the amount of drug that remains trapped because drug delivery is a function of surface area.